REMARKS

Claims 3-8 are all the claims pending in the application; claim 3 is rejected; claim 4 is objected to; claims 5-8 are allowed.

Claim 3 has been amended to state that the pharmaceutical composition described therein is for intravenous administration. Support for this amendment may be found at page 17, line 7 through page 18, line 2. Specific reference to continuous intravenous injection is found at page 17, lines 19-21.

Claim 9 has been added and is fully supported by the specification. Specific reference to dissolving the composition upon use may be found at page 19, lines 18-21. The ampoule preparation of the '884 application and the pharmaceutical composition recited in claim 9 are distinguished from each other with respect to 1) the condition of existence (solution in the case of the '884 application and solid in the case of the pharmaceutical composition to be dissolved upon use according to claim 9) and 2) the composition (solvent is contained in the case of the composition of the '884 application whereas no solvent is contained in the case of the pharmaceutical composition to be dissolved upon use according to claim 9).

No new matter has been added and entry of the amendment is earnestly solicited.

I. Rejection Under 35 U.S.C. §102(b)

At page 2 of the Office Action, paragraph 1, the rejection of claim 3 under 35 U.S.C. §102(b) as being anticipated by JPA 8-169884 ("the '884 application") is maintained.

The Examiner continues to assert that the cited reference teaches the use of a mGluR1 antagonist in a pharmaceutical formulation for the treatment of cerebral infarction. The

Examiner further states that the use of an old composition for a new purpose does not create a patentably distinct use.

In response, Applicants have amended claim 3 to distinguish the formulation of the pharmaceutical composition claimed therein from the formulation disclosed for the composition of the '884 application. While the '884 application is directed to an ampoule preparation for parenteral administration, claim 3 has been amended to state that the pharmaceutical composition is in a form for intravenous administration. Thus, because the '884 application does not disclose a formulation of the pharmaceutical composition recited therein for intravenous administration, the composition recited in claim 3 (as herein amended) is distinguished therefrom.

Applicants enclose a copy of page 7 of EP-A-787723, which corresponds to the '884 application, and refer to lines 24-26 for support of their position.

Applicants further note that for the treatment of acute stage ischemic stroke, it is important to allow the drug used for treatment to rapidly transfer to the brain and maintain the drug concentration in the brain. Therefore, the intravenous administration, in which a considerable amount of drug can be administered, is required. In other words, in the case of an ampoule preparation, the amount of drug which can be administered is limited to a small amount. Accordingly, the ampoule preparation is not suitable for use in the present invention.

Accordingly, the formulation of the pharmaceutical composition for intravenous administration according to the present invention is not described in the '884 application and thus novel. The pharmaceutical composition for intravenous administration can be further distinguished with respect to the content of the active ingredient.

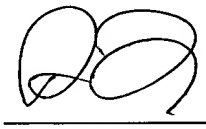
In view of these comments, and the amendment to claim 3, Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

3. (Thrice amended) A pharmaceutical composition for intravenous administration for treating acute stage ischemic stroke, which comprises a compound having mGluR1 antagonism in an amount effective for treating acute stage ischemic stroke by intravenous administration as an active ingredient and a pharmaceutically-acceptable carrier.

Claim 9 is added as a new claim.

By deallylation of any of the compounds (1a) to (1d) in which R^6 of the group $-OR^6$ represented by X^2 is 2-propenyl group according to the known method [A.B. Smith et al.: J. Am. Chem. Soc., 114, 9343 (1992)] in the presence of a catalytic amount of rhodium triphenylphosphine chloride complex, by hydrogenation of any of the compounds (1a) to (1d) in which R^6 of the group $-OR^6$ represented by X^2 is benzyl group or p-methoxybenzyl group in a solvent such as methanol, ethanol or isopropyl alcohol in the presence of a catalytic amount of Pd-C, or by treating any of the compounds (1a) to (1d) in which R^6 of the group $-OR^6$ represented by X^2 is methoxymethyl group, methoxyethoxymethyl group, or 2-(trimethylsilyl)ethoxymethyl group with an acid such as acetic acid, trifluoroacetic acid, hydrochloric acid or sulfuric acid, a compound represented by formula (1) whore R^6 of the group $-OR^6$ represented by X denotes a hydrogen atom can be obtained. Further, a compound represented by formula (1) whore R^3 of the group $-COOR^3$ represented by B is a hydrogen atom can be obtained by hydrolysis of any of the compounds represented by (1a) to (1d) by the known method.

Each isomer of the compound represented by general formula (1) can be separated by recrystallization, column chromatography, thin layer chromatography, high performance liquid chromatography, or the similar methods using optically active reagents.

The compounds represented by general formula (1) of the present invention have low toxicity and may be used alone or, if desired, prepared in combination with conventional pharmaceutically acceptable carriers to provide a pharmaceutical product for ameliorating and treating symptoms arising from various brain disorders. For example, the active ingredient may be prepared, alone or in combination with conventional vehicles into appropriate dosage forms such as capsules, tablets or injections and administered orally or parenterally. A capsule, for example, is prepared by the steps of admixing a bulk powder of the inventive compound with a vehicle such as lactose, starch, or a derivative thereof, or a cellulose derivative; and filling the mixture in gelatin capsules. A tablet is prepared by the steps of kneading the bulk powder, the aforementioned vehicle, a binder such as carboxymethylcellulose sodium, alginic acid or gum Arabic, and water; forming the kneaded mixture into granules if necessary; adding a lubricant such as talc or stearic acid; and then forming the mixture into tablets with a standard compression machine for forming tablets. For parenteral administration by injection, the active ingredient is dissolved along with a solubilizing agent in sterile distilled water or sterile physiological saline, and filled in ampoules. Other ingredients such as a stabilizer and a buffering agent may also be included in those formulations if necessary.

Dosage of the composition for treatment of functional or organic disorders provided by the present invention depends on various factors such as symptoms and age of the patient to be treated, route of administration, dosage form and frequency of administration, and is usually 0.1 to 1,000 mg/day/adult, preferably 1 to 500 mg/day/adult.

The present invention is further illustrated by the following examples which should not be interpreted as limiting the scope of the present invention.

Example 1. Synthesis of 1a-ethoxycarbonyl-1a,7a-dihydro-7(1H)-cyclopropa[b]chromen-7-one

To a suspension of 66 mg of sodium hydride in 6 ml of dimethylformamide in an ice bath, 363 mg of trimethylsulfoxonium iodide was added, and the mixture was stirred for 30 minutes at room temperature. Then 300 mg of 2-ethoxycarbonyl-4-oxo-4H-1-benzopyran was added, and the mixture was stirred for 15 minutes at room temperature. Ten ml of ice water was added subsequently to the reaction mixture, followed by extraction with ether. The extract was washed with a saturated sodium chloride aqueous solution, dried, filtered and then concentrated under reduced pressure to obtain a residue. The residue was purified by column chromatography on silica gel (hexane:ether=5:3), which yielded 143 mg of the above-referenced compound (yield: 45%).

Example 2. Synthesis of 1a-carboxy-1a,7a-dihydro-7(1H)-cyclopropa[b]-chromen-7-one

To a solution of 100 mg of the 1a-ethoxycarbonyl-1a,7a-dihydro-7(1H) -cyclopropa[b]chromen-7-one synthesized in Example 1 above in 4 ml of dioxane in an ice bath, 4 ml of a 10% sodium hydroxide aqueous solution was added dropwise, and the mixture was stirred for 2 hours at room temperature. The mixture in the ice bath was then adjusted to pH 3 with concentrated hydrochloric acid, followed by extraction with ether. The extract was dried, filtered and concentrated under reduced pressure to obtain crude crystals. Recrystallization thereof from ether/hexane yielded 80 mg of the above-referenced compound (yield: 90%).

Example 3. Synthesis of 1a-isobutoxycarbonyl-1a,7a-dihydro-7(1H)-cyclopropa[b]chromen-7-one

This compound was prepared in the same manner as that described in Example 1 from 2-isobutoxycarbonyl-4-oxo-4H-1-benzopyran.